Zika Virus: A Pandemic in Progress

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June 10, 2016
- Zika background
- Current outbreak in Caribbean and Latin America
- Zika and the USA
- Role of research and development
  - Basic science, epidemiology, natural history
  - Countermeasures: diagnostics, vaccines, therapeutics, vector control
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Zika Virus

- Single-stranded, enveloped RNA virus
- Family *Flaviviridae*, genus *Flavivirus*
- Closely related to dengue, yellow fever, Japanese encephalitis and West Nile viruses
- Transmitted to humans primarily by *Aedes* mosquito species

Source: CDC
Zika Virus.
I. Isolations and Serological Specificity

GW Dick, SF Kitchen, AJ Haddow

Virus first isolated from a monkey in the Zika forest of Uganda in 1947
Zika Virus: A Report on Three Cases of Human Infection During an Epidemic of Jaundice in Nigeria

FN MacNamara

March, 1954
Vol. 48 No. 2

First human cases reported in Nigeria in 1952
Zika Virus Outbreaks Beyond Africa, 2007-2014

Zika Virus Outbreak on Yap Island, Federated States of Micronesia
MR Duffy, TH Chen, EB Hayes, et al.

Zika Virus, French Polynesia, South Pacific, 2013
VM Cao-Lormeau, C Roche, D Musso, et al.
Zika Virus Spread, 1947-2016

1952: First human cases described

1947: Discovered in Uganda

1977-78: Pakistan, Malaysia, Indonesia

2007: Yap, Micronesia

2013: French Polynesia

2015: Brazil

Source: Lancaster University
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Countries and Territories with Active Zika Virus Transmission – June 2016

48 countries/territories (39 in the Americas/Caribbean)

Source: CDC, as of May 26, 2016
Microcephaly Attributed to Zika

Normal infant brain and head size

Microcephaly, Colombia 2015

Images: LatinAmericanScience.org
Guillain-Barré Syndrome Outbreak Associated with Zika Virus Infection in French Polynesia: A Case-Control Study

VM Cao-Lormeau, F Ghawché et al.

- 98% of 42 pts with GBS had anti-Zika virus IgM or IgG, and all (100%) had neutralizing antibodies against Zika virus compared with 56% of 98 pts in control group w/nAbs (p<0.0001)

- 88% of 42 patients with GBS reported symptoms of Zika virus infection ~6 days before onset of neurological symptoms

- Based on attack rate for Zika virus of 66% in French Polynesia, risk of GBS in the general population during the outbreak was 24 /100,000 infections
Acute Myelitis Due to Zika Virus Infection

S Mécharles, A Lannuzel, et al.

15-year-old girl in Guadeloupe, French West Indies with high concentrations of Zika virus in serum, urine, and cerebrospinal fluid
Zika Virus Associated with Meningoencephalitis

G Carteaux, I Leparc-Goffart et al.

- 81-year-old man in France with meningoencephalitis following cruise in the Pacific (area of New Caledonia, Vanuatu, the Solomon Islands, and New Zealand)

- CSF positive for Zika virus, by PCR and culture
Brazilian Scientists Find New Zika-linked Brain Disorder in Adults

- Autoimmune syndrome called **acute disseminated encephalomyelitis (ADEM)** seen in two patients with Zika virus infection

- Findings presented at the American Academy of Neurology meeting in Vancouver
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Potential for Imported Cases of Zika in the United States

- 216 million passenger journeys to U.S. annually from areas with local Zika virus transmission
  - 34 M by air
  - 173 M by land
  - 9 M by sea

Estimated Range of *Aedes aegypti* and *Aedes albopictus* Mosquitoes in the United States, 2016

Source: CDC
Dengue Cases in the United States, 2010-2015

50 states
- Travel-associated cases: 3,572
- Locally-transmitted cases: 292

Source: ArboNet. Includes provisional data for 2015.
Chikungunya Cases in the United States, 2014-2015

50 states

- Travel-associated cases: 3,478
- Locally-transmitted cases: 12

Source: CDC. Cases reported to ArboNET as of 1/12/2016.

0-21
Am. Samoa

Travel-associated cases: 695
Locally acquired cases: 1,301 (all in territories)

Source: CDC. Data as of 6/8/16.
Geographic Distribution of Laboratory-Positive Chikungunya Cases — Puerto Rico, May 5-August 12, 2014

Modalities of Transmission of Zika Virus

- Mosquito bites
- Sexual transmission
- Blood transfusion
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NIAID Countermeasure Research and Development

Therapeutics

Novel Vector Control

Vaccines

Diagnostics

Basic Research

Expansion of Research Capacity

Genomics

Clinical Research
Zika Virus in the Americas: An HHS Expert Consultation to Accelerate the Development of Countermeasures

March 28-29, 2016, Bethesda, Maryland

Goals

- Review current knowledge
- Identify critical research gaps
- Discuss ways to accelerate research

Supported by NIAID, NICHD, ASPR/BARDA, CDC and FDA
Biomedical Research Response: Basic Science

- Molecular Virology: a) elucidate viral structure; b) compare viruses from different outbreaks
- Pathogenesis of disease
- Studies on immune response (innate and adaptive)
- Establish animal models
Structure largely similar to that of other flaviviruses, except for notable difference in region of E glycoprotein that may be used for attachment to host cells.
Zika Virus Causes Microcephaly and Other Fetal Abnormalities in Mice

- **Cell**
  - Published online May 11, 2016
  - *Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise*
  - JJ Miner, MS Diamond et al.

- **Nature**
  - Published online May 11, 2016
  - *The Brazilian Zika Virus Strain Causes Birth Defects in Experimental Models*
  - FR Cugola, PC Beltrão-Braga et al.

- **Cell Stem Cell**
  - Published online May 11, 2016
  - *Zika Virus Disrupts Neural Progenitor Development and Leads to Microcephaly in Mice*
  - C Li, Z Xu et al.
Zika Virus Impairs Growth in Human Neurospheres and Brain Organoids

PP Garcez, SK Rehen et al.

Control  Zika-virus infected neurosphere
Biomedical Research Response: Epidemiology and Natural History

- Epidemiology and natural history
  - Symptomatic vs. asymptomatic
  - Frequency of sequelae
  - Cohort studies to determine incidence of adverse pregnancy outcomes in Zika-infected pregnant women

- Pathogenesis of microcephaly
Biomedical Research Response: Diagnostics

- CDC – Diagnostic and Reference Laboratory in Arbovirus Diseases Branch

- RT-PCR assay for Zika, Dengue and Chikungunya

- Antibody assay for acute infection that will not cross-react with other flaviviruses
Developing Improved Diagnostics Through Mutagenesis

Zika → Cross-reactive epitopes → Mutagenesis → Zika with reduced cross-reactivity

Dengue
Biomedical Research Response: Countermeasures – Therapeutics

- Developing *in vitro* antiviral screening assay

- Testing compounds with known activity against other flaviviruses

- Broad screening of compounds without known anti-flavivirus activity
**Zika Vaccine Development Timeline**

- **2016**
  - DNA vaccine candidate (NIAID VRC): Preclinical Discovery
  - Whole-particle inactivated virus (NIAID/WRAIR/BARDA and corporate partner): Preclinical Discovery
  - Live-attenuated Zika/dengue chimeric virus (NIAID intramural/Butantan): Preclinical Discovery
  - Vesicular Stomatitis Virus vectored vaccine (NIAID extramural): Preclinical Discovery/Tech Transfer
  - mRNA vaccine candidate (NIAID VRC): Preclinical Discovery

- **2017**
  - DNA vaccine candidate (NIAID VRC): Phase 1
  - Whole-particle inactivated virus (NIAID/WRAIR/BARDA and corporate partner): Phase 1
  - Live-attenuated Zika/dengue chimeric virus (NIAID intramural/Butantan): Phase 1
  - Vesicular Stomatitis Virus vectored vaccine (NIAID extramural): Phase 1
  - mRNA vaccine candidate (NIAID VRC): Preclinical Discovery

- **2018**
  - DNA vaccine candidate (NIAID VRC): Long term follow up
  - Whole-particle inactivated virus (NIAID/WRAIR/BARDA and corporate partner): Long term follow up
  - Live-attenuated Zika/dengue chimeric virus (NIAID intramural/Butantan): Phase 2
  - Vesicular Stomatitis Virus vectored vaccine (NIAID extramural): Phase 1
  - mRNA vaccine candidate (NIAID VRC): Phase 1

- Intramural NIAID and partnerships
- Extramural NIAID and partnerships
- Preparation for clinical trials
DNA Vaccine Approach

Gene encoding surface protein from Zika virus

Inject DNA containing Zika gene

Body’s cells produce virus-like particles, the basis of the vaccine

Plasmid

Muscle cell
DNA Vaccine Development Timeline

2016
- Pilot scale manufacturing (NIAID Vaccine Research Center Pilot Plant, Frederick MD)
- Small animal testing
- Non-human primate testing

2017
- Initial safety and immunogenicity data
- Phase 1 US multi-center settings (Zika naïve)

2018
- Phase 2/2b (multiple sites in Southern US, Caribbean, Central and S. America, age range 18-35)
- Long term follow up
Vaccination for Congenital Infections: Lessons from Rubella

- 1964-65 U.S. rubella epidemic
  - 11,000 miscarriages, 2,100 newborn deaths, 20,000 babies born with congenital rubella syndrome (CRS)
- CRS causes deafness, cataracts, heart defects, often microcephaly
- With MMR vaccine, CRS eliminated in U.S. in 2004
Emerging Infections: A Perpetual Challenge

DM Morens, GK Folkers & AS Fauci